Applicants acknowledge Examiner's objection for Claims 13 and 18; in order to advance examination these claims have been deleted.

The state of the art and the predictability or lack thereof in the art.

The Examiner states that the pharmacological art involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat which specific diseases by what mechanism).

Applicants agree with the fact that screening is the tool used in the art of pharmacology.

Applicants respectfully disagree with the statements:

a) *"There is no absolute predictability even in view of seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic or preventive agent in its face".*

b) *"In addition, there is no established correlation between in vitro or in vivo activity and accomplishing treatment of various diseases, and those skilled in the art would not accept allegations in the instant specification to be reliable predictors of success, and those skilled in the art would not be able to use the compounds of formula (I), since there is no description of an actual method wherein various tumors in a host is treated".*

According to the MPEP, a reasonable basis must be established on the record for a proper rejection under this Section. Reasonable basis has not been established.

> "When basing a rejection on the failure of the applicant's disclosure to meet the enablement provisions of the first paragraph of 35 USC §112, USPTO personnel must establish on the record a reasonable basis for questioning the adequacy of the disclosure to enable a person of ordinary skill in the art to make and use the claimed invention without resorting to *undue experimentation.* See *In re Brown*, 477 F.2d 946, 177 USPQ"

Respecting the spirit of the law, an inventor must enrich the state of the art, as said below:

> "The grant of a patent helps to foster and enhance the development and disclosure of new ideas and the advancement of scientific knowledge. Upon the grant of a patent in the U.S., information contained in the patent becomes a part of the information available to the public for further

REMARKS/ARGUMENTS

Elected/Examined Subject Matter

Applicants wish to correct/clarify their response of May 20, 2008. In the response, Applicants elected Group II, with the elected species being the compound (Z)-1,2-difluoro-1-(3,4,5-trimethoxyphenyl)-2-(3-hydroxy-4-methoxyphenyl)ethane o-disodium phosphate (ST2493). Now, Applicants realize that it was their true intention to elect Group I, namely compounds wherein the variable R' is not $(COCHR"NH)_n$-H, as the elected compound clearly shows. In other words, the elected group is inconsistent with the elected compound. As it appears the search conducted to date was directed to the elected compound. Applicants believe there will be no difficulty or inconvenience in shifting attention to the Group I compounds.

To this end $(COCHR"NH)_n$-H is deleted from claims 1 and 2.

Discussion of Claim Amendments

Claim 1 has been amended by deleting the meaning of H for the groups R_1, R_2 and R_3 and to adopt the terminology suggested by the examiner for the last line of the claim (singular) in item 7 of the Action.

Claim 4 is amended to adopt the format/style suggested by the examiner in item 4 of the Action.

Claim 13 has been cancelled without prejudice or disclaimer.

Claim 14 directed to known tumors has been made dependent from claim 1.

Claims 15-16 have been deleted without prejudice or disclaimer.

Claim 17 has been made dependent from claim 1 to advance prosecution.

Claim 18 has been deleted without prejudice or disclaimer.

Claim 20 has been made dependent from claim 1 to advance prosecution.

Claim 21 has been added.

Response to the Rejection of Claims 13-18 and 20 – 35 U.S.C. 112, First Paragraph – Lack of Enablement

Cancellation of Claims 13, 15-16 and 18 renders the objection moot as to these claims. The remaining claims are enabled by the specification. However, for sake of clarity, Applicants wish to support enablement of the Claims with the arguments below.

The nature of the invention.

> research and development, subject only to the patentee's right to exclude others during the life of the patent."
>
> As said:
>
> "discussed in more detail below, the patentee must disclose in the patent sufficient information to put the public in possession of the invention and to enable those skilled in the art to make and use the invention."

According to the MPEP, a patent need not to teach, and preferably omits, what is well known in the art. And, the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation.

As to the examiner's statement a) above, Applicants respectfully disagree. The pharmacological art is statistic-based. The examiner, as a knowledgeable person in this art, is also aware that pharmaceutical patents on new chemical entities are granted not on the basis of a complete cycle of development, namely after completion of Phase III trials, as required by regulatory authorities, such as the FDA or the EFPIA. Otherwise, a patent application should be filed after at least five or six years of experimentation and unavoidable disclosure of the invention to the public. It would be an invalid application.

Persons skilled in the art of pharmacology customarily accept minimum evidence to carry out an invention in this field.

The evidence provided in the subject application is more than sufficient, and the relevant facts are herein listed.

The art in cancer chemotherapy has demonstrated that drugs which disrupt microtubule synthesis are effective in inhibiting the proliferation of neoplastic cells (Specification, page 1, 1st, 2nd paragraph).

Combretastatin A-4 (CA-4) shows exciting potential as an anticancer agent binding strongly to tubulin at a site shared with, or close to, the colchicine binding site (*Lin, C.N., et al; Biochemistry, 1989, 28, 6984*) and shares many structural features common to other tubulin-binding agents such as colchicine and podophyllotoxin. The phosphate salt [CA-4P] (*Pettit, G.R., et al.; Anticancer Drug Des., 1995, 10, 299*), which has better water solubility than CA-4, has entered Phase II clinical trials. (Specification, page 1, 3rd and 4th paragraph).

It is the ability of combretastatins to damage tumor vasculature, thereby effectively starving tumors of nutrients, which makes them such exciting molecules. Recently many studies have shown that a number of antiangiogenic agents, like CA-4P, can inhibit retinal neovascularization in a well-characterized murine model of ischemia-induced proliferative retinopathy. These studies suggest that as CA-4P or new derivatives as other antiangiogenic agents, could be useful in the treatment of non-neoplastic diseases like ischemia-induced proliferative retinopathy (*Griggs, J., et al., Am. J. Pathol., 2002, 160(3), 1097-103*). (Specification, page 2, 1st-3rd paragraphs).

The spatial relationship between the two aromatic rings of combretastatin, colchicine and similar drugs is an important structural feature that determines their ability to bind to tubulin (*McGown, A.T., et al., a) Bioorg. Med. Chem. Lett., 1988, 8(9), 1051-6; b) Bioorg. Med. Chem. Lett., 2001, 11(1), 51-4*) (Specification, page 2, 5th paragraph).

The present Applicants found that without any modification of the cis-stilbene motif the introduction of fluorine atom in olefin bond allows the biological activity to increase or, in case of the same activity, to influence the pharmacodynamics activity (Specification, page 2, 5th paragraph).

The working examples show the claimed compounds wherein:

- X = Y = F; R = OPO_3Na_2: difluorocombretastatin;
- X = Y = F; R = NH_2: difluoroaminocombretastatin;
- X = H; Y = F; R = OPO_3Na_2: monofluorocombretastatin;
- X = H; Y = F; R = NH_2: monofluoroaminocombretastatin;
- X = F; Y = H; R = NH_2: monofluoroaminocombretastatin;
- X = Br; Y = F; R = OPO_3Na_2: bromofluorocombretastatin.

And the working examples show the effects of representative compounds of the invention for cytotoxicity, tumor growth and tubulin polymerisation inhibition.

Contrary to Examiner's allegation, the array of information provided in the specification enables the skilled person to determine that the claimed compounds are effective in inhibiting tubulin polymerization and, in view of the knowledge provided by the art, also cited in the specification, the claimed compounds are cytotoxic, hence antitumor agents. A panel of tumor cell lines has been successfully tested and an in vivo test has been provided. In view of the

knowledge of the art, the skilled person, on the basis of tubulin polymerization test, is also able to perform the invention in the field of angiogenesis. In fact, the working example in the specification shows the efficacy of the claimed compounds also on endothelial cells (BMEC and HUVEC).

Absolute unpredictability, as alleged by the Examiner, in the context of the present invention, becomes a concept which is not supported by the effective witness of the art. Applicants cited the art of combretastatin and its derivatives and also showed that a Phase II trial was started (see above). The information provided in the specification, both taken from the art and those coming from the invention, allows the skilled reader to determine that the claimed compounds, having proved to be active in inhibiting tubulin polymerization and in view of the structural requirements given by the art, are active in the field they are expected to be, namely in tumors and in altered angiogenesis pathological states. In *Chiron Corp. v. Genentech Inc., 363 F.3d 1247, 1254 70 USPQ2d 1321, 1326 (Fed. Circ. 2004): "Nascent technology, however must be enabled with a 'specific useful teaching'*. Applicants respectfully submit that pharmacology is not a nascent technology. Applicants would dare to say that pharmacology dates back from ancient times, and modern pharmacology, based on the predictability of *in vitro* test is a well-established practice. On the basis of such a successful test, the skilled person is prompted to develop the invention through the standard steps of drug development, for example as provided in the FDA Rules.

The claimed compounds are shown to have multiple uses, namely antitumor agents and antiangiogenesis agents. The specification provides experimental evidence on any of these uses, therefore the claims shall be considered enabled, see MPEP 2164.01(c) (*if any use is enabled when multiple uses are disclosed, the application is enabling for the claimed invention*).

As to the examiner's statement b) above, the Examiner will note that the application presents working, and not prophetic examples.

According to MPEP, initial burden is on the Examiner to give reason for lack of enablement and for conclusions of lack of correlation for an *in vitro* or an *in vivo* animal model example.

Applicants used models accepted in the general knowledge of pharmacology. If required, Applicants will provide the Examiner references from the scientific literature. If the art

recognizes that particular model is recognized as correlating to a specific condition, then its should be accepted as correlating unless the Examiner has **evidence** that the model does not correlate (see MPEP and *in re Brana* and *Cross v. Iizuka*). Applicants are anxious to obtain a valid patent, therefore, if the Examiner produces such evidence jeopardizing allowability of the claims, Applicants will eagerly reconsider their position in order to limit the subject-matter to a valid claim. At present, Applicants wishes to discuss, and in case accept, Examiner's position, but on the basis of sound evidence.

The Markush group of Claims 14 and 17 is a genus sufficiently supported by the working examples.

At the moment, Applicants invoke presumption of compliance of the claimed subject-matter with 35 U.S.C. § 112, first paragraph.

To conclude the issue of the state of the art and the predictability or lack thereof in the art, Applicants would like to consider the required specific technical reasons which lead the Examiner to reject the claims under this Section (see MPEP 2164.04).

The amount of direction or guidance present and the presence of working examples.

The presence of working examples has been established above. The claims now on record are limited, therefore this part of the rejection is now moot.

The breadth of the claims.

In view of the above, the claims are now limited and enabled by the specification.

The quantity of experimentation needed.

The claims now on record are enabled by the specification. The skilled in the art has only to apply the invention to any of the tumors listed in Claim 14 or the diseases of Claims 17 and 20. All these diseases are shown in the art to be effectively treated by combretastatin. Therefore there is no reason to believe in an undue burden of experimentation. It is to be noted that the experiments used in the present application are all merely routinary experiments and also easy to perform.

The level of the skill in the art.

Correctly, the Examiner affirmed the high level of the skilled in the art. Because of his/her level, this person is able to perform the invention. The specification provides adequate

background art to avoid that each embodiment be individually assessed for physiological activity.

The claims now recite a limited number of diseases, each known to be treated by tubulin polymerisation inhibitors, in particular by combretastatin and its derivatives. Upon the Examiner's request, Applicants are ready to provide evidence from the art.

Applicants deem that now the claims on record do not fall in the jurisprudential circumstance of *Genentech v. Novo Nordisk*, since the presently claimed invention successfully concluded that fluoroderivatives of combretastatin have medical utility in a well-defined set of diseases.

As completeness to the argument of the level of the skill in the art, a selection of papers[1] demonstrating the level of skill in this art are attached.

Literature references

As regards claim 14:

Bone tumor:

Neuroendocrine tumor

Lymphoid leukaemia: *Anti-Cancer Drugs*, **2000**, *11*, 5, 385 (to be provided)

Acute promyelitic leukaemia: *Clin. Canc.*, **2002**, *8*, 2735

Myeloid leukaemia

Monocytic leukaemia

Megakaryocytic leukaemia

Non Hodgkin's disease: *Anti-Cancer Drugs*, **2001**, *12*, 57

Hemangiomas

Multiple myeloma

Anaplastic thyroid cancer: *Canc. Res.*, **2002**, 3408; *B. J. C:*, **2001**, 832

As regards claim 17

Arthritic disease

Diabetic retinopathy: *Am. J. Pathol.*, **2002**, 1097

Macular degeneration: Inves. Opht & Vis. Science, **2003**, *44*, 8, 3650

[1] These papers are also listed on the attached form PTO/SB/08A so the record of this application will show that this information was considered.

Psoriasis

Chronic inflammation disease

Atherosclerosis: *Nat. Prod. Rep.*, **2003**, *20*, 558

Response to Rejection of Claims 1-10 and 13-20 Under 35 U.S.C. 102(b)

Amendment of Claim 1 overcomes the rejection. The claims are now free of prior art.

In view of the above considerations and the presented amendments, Applicants respectfully request withdrawal of rejection and allowance of this application.

Respectfully submitted,

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